REMARKS

This Response is filed to the Office Action dated June 3, 2002. Claims 20-25 and 56-81 are pending. Claims 1-20 and 26-55 were previously cancelled without prejudice or disclaimer. Claims 56-58, 60-62, 67-68, 71-76, and 79-80 were rejected and Claims 59, 63-66, 69-70, 77-78, and 81 were objected to as being dependent upon a rejected base claim, but has indicated that these claims would be allowable if rewritten in independent form. In response, Applicants have cancelled Claims 57-59, 68, 71-75, 77 and 79-80 and have amended Claims 56, 60, 63, 66, 67, 70, 76 and 78 to further define various features of Applicants' invention. Applicants have also added Claims 82-84, which are similar to previous claims and present no new matter. Applicants have also added Claim 85, which additionally presents no new matter. Applicants respectfully request reconsideration and favorable action in this case.

Interview

Applicants thank Examiner Leary for her telephone interview on October 21, 2002 with Attorney for Applicants, Michelle LeCointe, and Scientific Advisor, Kate Musemeche, both of Baker Botts, L.L.P. During the interview the Cook reference was discussed. In particular, the precise disclosures present or not present in the reference were discussed. Agreement on the issue was not reached. Further comments in response to the outstanding Office Action as well as issues raised during the interview are presented below.

Applicants also thank Brian Stanton, Practice Specialist, Technology Center 1600 for a telephone interview with Attorney for Applicants, Michelle LeCointe on October 22, 2002 during which the Cook reference and the Examiner's arguments were discussed and the matter was referred to Brenda Brumback, supervisor for Group 1654.

Applicants additionally thank Brenda Brumback, Group 1654 for a telephone interview with Attorney for Applicants, Michelle LeCointe on October 30, 2002 during which the Cook reference and the Examiner's arguments were discussed. Ms. Brumback suggested that Applicants provide an additional response further describing the deficiencies in Cook.

Rejections

The Examiner has rejected Claims 56-58, 60-62, 67-68, 71-76, and 79-80 under 35 U.S.C. §102(b) as being anticipated or, alternatively, under 35 U.S.C. § 103(a) as being obvious in light of US Patent 3,928,594 (Cook).

Cook teaches "new therapeutic uses of cholinesterase reactivators for the symptoms and signs associated with demyelinating processes . . ." (col. 1, lines 4-6). These conditions in man are characterized by acetylcholine-cholinesterase imbalance. (col. 1, lines 7-9). In contrast, Applicant teaches "methods and diagnostic kits for providing an objective diagnosis of pain or stress experienced by a patient, and to compositions and methods for the alleviation of pain or stress." (p.1, lines 9-11).

The Examiner has stated that "Cook discloses a method of diagnosing the intensity of pain in a patient comprising determining the amount of cholinesterase in a biological sample from the patient." (Office Action 6/30/2002, p3, para.1). The Examiner, however, does not give a pinpoint cite for this statement. In a phone interview with the Examiner (October 21, 2002 – Louise Leary, Michelle LeCointe and Kate Musemeche) to ask for a cite to support this statement, the Examiner did not give one. Rather, the Examiner referred to column 4, lines 2-5 which states: "Comparative evaluation was permitted." Examiner stated that this sentence alone could indicate that serum cholinesterase levels were measured in Cook's study population, even though Cook does not explicitly state that he measureded serum cholinesterase levels or diclose a method for doing so.

After treating patients with 2-PAM-Cl Cook states that he"observed" the clinical effects of treatment such as alertness, mental depression, function of the voluntary motor system, ataxia and relief of pain. (col. 4, lines 5-41). The term "clinical effects" generally refers to sign of symptoms, not laboratory values. In a later summary of his findings, Cook states "The significant effect in demyelinating diseases of compounds capable of changing the chemical constitution of cholinesterase *suggests* that a major effect in the symptomotology depends upon the degree of change in the chemistry of cholinesterase. (col. 4, lines 53-57, emphasis added).

Cook does not explicitly state that he measured cholinesterase levels in his experimental subjects. Applicant claims a method of diagnosing the extent of activation of the pain sensing neuroligcal pathway in a patient comprising determining the amount of pain marker in a biological sample obtained from said patient . . ." (Claim 56). Cook neither describes nor discloses measuring a pain marker in a biological sample. Thus Cook does not teach all claim limitations of Applicant's Claim 56.

The Examiner objected (Office Action 6/20/2002) that Cook discloses methods of diagnosing the intensity of pain perceived by a patient comprising determining the amount of neurotransmitter or cholinesterase citing column 4, lines 2-5 which states "Comparative evaluation was therefore permitted." This sentence follows Cook's description of a group of patients given a placebo that could be compared to the study group who received 2-PAM-Cl. Again, Cook does not disclose measuring a pain marker in a biological sample in either the study group or the control group. Furthermore, the standard way of measuring pain at the time Cook was written and even today involves a series of subjective questions, not an actual measurement of a biological sample. Cook does not disclose a method of evaluating pain intensity. He merely states that patients were "observed."

One of skill in the art at the time the present application was filed and at the time Cook was filed would not assume that "observing" a patient involves evaluation of pain intensity, especially in a disease such as multiple sclerosis where many symptoms are indicative of the disease state. Additionally, even if such observation did include pain analysis, objective analysis of biological markers was not common at the time Cook was filed. Rather, pain analysis involved subjective questions. Accordingly, even if Cook's observations would be assumed by one skilled in the art to include pain analysis, one skilled in the art would expect such analysis to involve subjective questions and not measurement of a biological marker. Applicants have provided ample support for the use of subjective analysis as the state of the art in pain measurement even as late as the time of filing of the present application in both the background portion of the specification and in references cited in Applicants' Information Disclosure Statement.

In light of the above remarks and Applicants' previous arguments, Applicants assert that Cook fails to disclose or suggest any objective measurements of a biological marker for pain. By not pointing out an explicit statement in Cook, the Examiner is asking Applicants to prove a negative. If, as the Examiner asserts, Cook does include measurement of a biological marker, then Applicants would greatly appreciate a pinpoint cite to such, indicating that Cook alone or in combination with other prior art indicates that one skilled in the art would read Cook in such a manner. Applicants further request a prior art reference supporting any assumptions required to assert that Cook discloses measurement of a biological marker. The Examiner has not provided such information and merely asserts that one would assume that Cook used objective measurements. Applicants once again assert that, absent something more than a statement of what one would assume that does not follow from strict logic or actual factual evidence, the Examiner has failed to set forth a prima facia case of obviousness as required under 35 U.S.C. §103(a).

Allowable Claims

The Examiner has objected to Claims 59, 63-66, 69-70, 77-78, and 81 as being dependent upon a rejected base claim, but has indicated that these claims would be allowable if rewritten in independent form. Claims 21-25 were deemed allowable over the prior art record.

Amendments

Claims 56, 60, 63, 66, 67, 70 and 76 have been amended to include material indicated to be allowable. As a result, these claims should be allowable and free of any art rejections.

CONCLUSION

Based on the foregoing remarks, Applicants submit that the present application is in condition for allowance. A Notice of Allowance is therefore respectfully requested.

Applicants believe a fee in the amount of $460.00 (small entity) is required for a three month extension of time under 37 C.F.R. 1.17(a)(3). Applicants believe no additional fees are

due. Should any additional fees be due for this or any other communication, the Commissioner is hereby authorized to charge Deposit Account Number 50-2148.

If there are any matters concerning this application that may be cleared up in a telephone conversation, please contact Applicant's attorney at 512.322.2581.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Please amend Claims 56, 60, 63, 66, 67, 70, 76 and 78 as set out below.

56. (Once Amended) A method of diagnosing the extent of activation of the pain sensing neurological pathway in a patient comprising:

i) determining the amount of a **cholinesterase** pain marker in a biological sample obtained from said patient;

ii) comparing the amount of the **cholinesterase** pain marker in said sample to **[at least one pre-determined] a threshold amount of cholinesterase** pain marker **[amount]**; **and**

iii) assigning a pain status to the patient based upon the comparison, **wherein the threshold amount of cholinesterase pain marker is determined by measuring the amount of cholinesterase in samples from patients in whom the pain sensing neurological pathway is not activated and setting the threshold so that the threshold amount of cholinesterase pain marker is at least three standard deviations above the mean cholinesterase amount in samples from normal individuals.**

60. (Once Amended) The method of claim **[58] 56**, wherein additional **amounts of** cholinesterase **[amounts] pain marker** are **[set] identified** as indicative of increasing levels of pain sensing neurological pathway activation by comparing the mean **[or average] amount of** cholinesterase **pain marker [amounts of] in** individuals with higher levels of pain sensing neurological pathway activation with mean **[or average] amount of** cholinesterase **pain marker [amounts of] in individuals with** lower levels of pain sensing neurological pathway activation and selecting an amount between the two means**[or averages]**.

63. (Previously Added) The method of claim 62, wherein the **[pre-determined serum cholinesterase]** threshold amount **of cholinesterase pain marker** is 1272 and patients from whom the sample contains less than this amount of serum cholinesterase are deemed to have normal activation levels of the pain sensing neurological pathway while patients from whom the sample contains greater than this amount of serum cholinesterase are deemed to have high or activated activation levels of the pain sensing neurological pathway.

66. (Once Amended) The method of claim **[57]** **56**, wherein the cholinesterase in the biological sample is reacted with a substrate to produce a detectable product.

67. (Once Amended) The method of claim **[57]** **56**, wherein the **[pre-determined]** **threshold amount of** cholinesterase **pain marker** **[amount]** is based upon **a normal individual sample** **[at least one biological sample of the same type]** **obtained** from the same patient **[obtained]** prior to **[the diagnosis of]** activation of the pain sensing neurological pathway.

70. (Once Amended) The method of claim **[57]** **56**, whereby cholinesterase may be distinguished and measured by eserine sensitivity.

76. (Once Amended) A diagnostic kit for determining the level of activation of the pain sensing neurological pathway in a patient comprising at least one **[agent]** **antibody** that **[reacts with]** **binds to** cholinesterase in a biological sample obtained from **[a]** **the** patient wherein the amount of cholinesterase in the sample is then compared with an amount of cholinesterase known to be indicative of activation of the pain sensing neurological pathway.

78. (Once Amended) The diagnostic kit of claim **[77]** **76**, wherein the antibody or antibodies are polyclonal antibodies, monoclonal antibodies or fragments of polyclonal or monoclonal antibodies.